Kidney International, Vol. 59 (2001), pp. 17–30

PERSPECTIVES IN BASIC SCIENCE

Regulation of renal tubular secretion of organic compounds

Efim B. Berkhin and Michael H. Humphreys

Division of Nephrology, San Francisco General Hospital, University of California San Francisco, San Francisco, California, USA

Regulation of renal tubular secretion of organic compounds.

Background. Information on the molecular basis underlying organic anion and cation transport in renal tubules has expanded in recent years with the identification and characterization of numerous transporters. However, little is known about the regulation of this transport.

Methods. Both English and Russian language studies dealing with the regulation of organic ion transport by the kidney have been reviewed.

Results. This review summarizes the literature on the physiological and pharmacological aspects of the regulation of organic ion transport, linking this information where possible to underlying transport mechanisms. Current models of the tubular secretion of organic anions and cations are reviewed. Factors that inhibit or enhance tubular secretion of xenobiotics are described, and their influence on proximal tubule cell transport and function is discussed. Important roles for substrate stimulation, the adrenergic nervous system, numerous hormones, P-glycoprotein, and protein kinase C activity have been identified.

Conclusions. Despite considerable advances in the understanding of basic transport pathways and mechanisms involved in the tubular secretion of organic compounds, there is still relatively little information on the regulation of this transport. Studies combining the techniques of integrative and cell physiology and molecular biology will provide significant new insights into the pathways regulating the tubular transport of these compounds.

The renal tubular transport of organic substances plays an essential role in the removal of xenobiotics, such as drugs, numerous chemicals contained in our environment, and some metabolites out of the body. The mechanisms mediating tubular secretion have been intensively studied over the past several decades, and the features of organic anion and cation transport, the nature of carriers and their interaction with substrates, and the forces driving transport through basolateral and luminal membranes have been characterized [1–5]. This information has recently been extended by the identification, using molecular cloning techniques, of specific transport proteins, which mediate the translocation of organic anions and cations across cell membranes to result in net vectorial secretion into the tubular lumen. Regulation of these processes has great practical significance, since suppression of tubular secretion may increase the exposure of the body to potentially dangerous synthetic and natural xenobiotics, while on the other hand, stimulation of tubular transport may be useful for prevention or treatment of occupational diseases by elimination of environmental toxins. The present review therefore briefly summarizes the literature on the physiological and pharmacological aspects of the regulation of tubular secretion, and reviews recent information on the transport proteins that carry out this tubular transport.

Key words: anion and cation transport, cellular transporters, neural control, cardiac glycosides, diuretics, protein synthesis, antineoplastic agents, immunomodulators.

Received for publication October 6, 1999
and in revised form July 6, 2000
Accepted for publication July 17, 2000

PHYSIOLOGICAL ASPECTS OF THE REGULATION OF RENAL ORGANIC ANION AND CATION TRANSPORT

Cellular transporters and their regulation

Specific transport proteins transfer organic compounds into tubular fluid. The best studied is the multidrug transporter P-glycoprotein. P-glycoproteins are proteins isolated from cell membranes, and they possess ATPase activity. They belong to a superfamily of transport proteins that contain an adenosine 5′-triphosphate (ATP) binding cassette. Other family members include the multidrug resistance (MDR)-associated proteins Mrp1 and Mrp2 and the multispecific organic anion transporter (MOAT). They are often called MDR proteins because they hasten removal of cytotoxic drugs from the cell interior and thus are associated with resistance of tumor cells to the action of these drugs [reviewed in 6–10]. The physiological role of P-glycoproteins may be in the protection of the organism from xenobiotics [8, 9]. In proximal tubule epithelium, P-glycoprotein is normally expressed on the apical membrane of cells [11], where it can mediate transport into the tubular fluid (Fig. 1). Numerous drugs are secreted into the tubular lumen through the P-glycoprotein pathway independent of or in addition to the organic anion and cation secretory

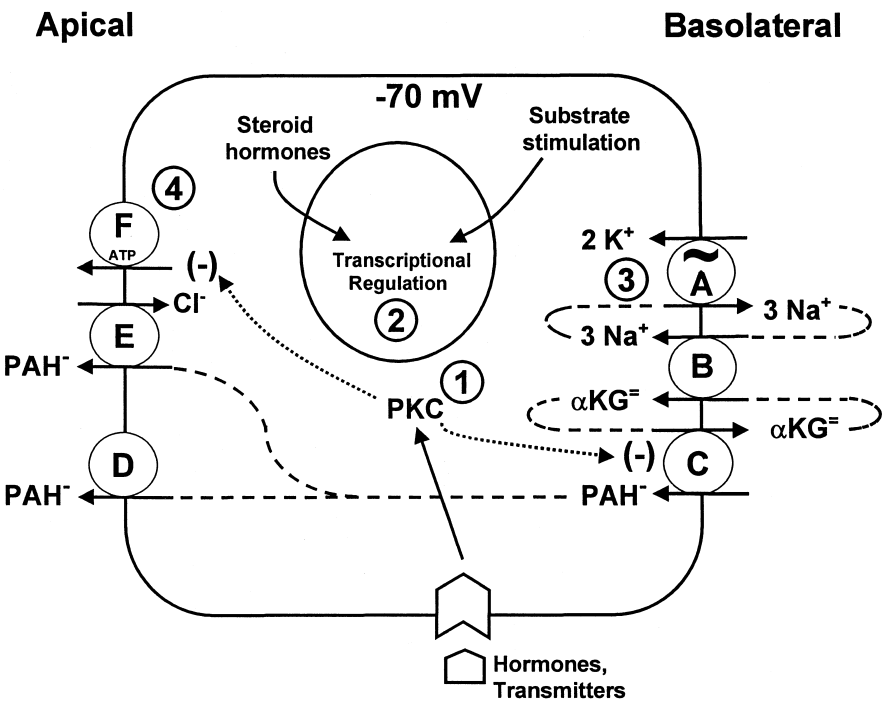

Fig. 1. Schematic diagram of the pathways involved in organic anion transport by proximal tubule cells, and the major sights of regulation of transport. Transport proteins are indicated by open circles with arrows showing the direction of transport. Individual components of transport are indicated by the letters. The electrogenic basolateral Na^+,K^+-ATPase (A) maintains the out > in Na^+ gradient and the cell interior negative with respect to the outside. Na^+ moves into the cell down this electrochemical gradient with α-ketoglutarate ($\alpha KG^=$) (B). $\alpha KG^=$ then exchanges with organic anions via the organic anion transporter (OAT); (C); para-aminohippurate (PAH^-) is used, for example. $\alpha KG^=$ then cycles back into the cell via pathway (B). PAH^- traverses the cell to the apical lumen, or enters into cytoplasmic vesicles (data not shown). Secretion of PAH^- into the tubular lumen occurs by facilitated diffusion down its electrochemical gradient (D) or by anion exchange (E). Some organic compounds undergo secretion into the lumen via multidrug resistance-associated protein 2 (Mrp2) located in the apical membrane (F) in a process utilizing ATP. Mechanisms of regulation of transport are shown by the numbers in circles. Increased activity of protein kinase C (PKC) resulting from actions of hormones and transmitters (1) leads to inhibition of OAT- and Mrp2-mediated transport. Nuclear acting mechanisms include steroid hormones and substrate stimulation, which alter transcription to increase the amount of transporter protein synthesis (2). Inhibitors of Na^+,K^+-ATPase (3) alter organic anion transport indirectly by reducing the Na^+ gradient. Finally, many compounds inhibit Mrp2 activity (4), discussed in the text. Modified with permission from PRITCHARD JB: Renal handling of organic acids and bases, in *Textbook of Nephrology* (4th ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Lippincott Williams and Wilkins (in press).

pathways described later in this article. These include digoxin [12], quinolone antibacterial drugs [13], rapamycin [14], and colchicine and other agents [9]. In the case of rapamycin, transport can be inhibited by cyclosporine A (CsA) and other substrates for P-glycoprotein, but not by para-aminohippurate (PAH) or tetraethylammonium (TEA) [14], compounds that are secreted by the organic anion and cation pathways (described later in this article). In the case of quinolone compounds, interactions with these anion and cation transport steps have also been demonstrated in addition to P-glycoprotein transport [15]. The mechanism by which P-glycoprotein mediates drug secretion is not entirely clear, but existing data support a drug pump model [9]. Many drugs, called chemosensitizers, antagonize MDR and thereby improve the effect of chemotherapeutic antitumor agents. Among them are calcium channel blockers, steroids (such as progesterone), and immunosuppressants, most notably CsA [16], which is the principal drug used for immunosuppression in organ transplant patients. CsA acts by binding to P-glycoprotein [17] and inhibits the tubular transport of vinblastine and vincristine [18] as well as digoxin [19].

Mrp2 is also located in high concentration in the brush border of proximal tubular cells [20] and shares many properties with P-glycoprotein. However, substrate specificities differ, with P-glycoprotein transporting primarily uncharged and cationic species, while Mrp2 transports conjugated anionic compounds [21, 22]. In addition, there is only approximately 25% amino acid homology between Mrp2 and P-glycoproteins [21, 23].

Organic anions are transported into the tubular cell across the basolateral membrane in a process energized indirectly by the sodium gradient. In a current model, sodium enters the cell with α-ketoglutarate, driven by the sodium gradient (Fig. 1). This is followed by α-ketoglutarate/organic anion exchange, transferring the organic anion into the cell. Ongoing cellular metabolic

Table 1. Some characteristics of cloned organic anion and cation transporters

Transporter	Source	Amino acids	Membrane localization	Main substrates	References
Anion transporters					
rOAT1, rROAT1	Rat kidney	551	Basolateral	PAH	[29, 30, 35, 59]
NKT (mOAT1)	Mouse kidney	546		PAH	[31]
fROAT1	Winter flounder kidney	562	Basolateral	PAH	[32]
hOAT1 (hPAHT)	Human kidney	563, 550	Basolateral	PAH, nucleoside phosphonates	[28, 33, 34, 36]
hOAT3	Human kidney	568	Basolateral	PAH	[34]
oatp	Rat liver, kidney		Basolateral, apical	Bromosulfothalein	[37]
OAT-K1	Rat kidney, renal cell line	669	Apical, basolateral	Methotrexate	[38, 39]
OAT-K2	Rat kidney	498	Apical	Methotrexate, taurocholate	[40]
Cation transporters					
rOCT1	Rat kidney, liver, intestine	556	Basolateral	TEA, methyl-phenylpyridinium	[41]
rOCT1A	Rat kidney, intestine	430		TEA	[41, 43]
rOCT2	Rat kidney	593		TEA	[45]
rbOCT1	Rabbit liver, kidney, intestine	554		Methylphenyl-pyridinium	[55]
hOCT1	Human liver, renal cell line	554	Apical	TEA	[44, 46]
hOCT2	Human liver	555	Apical	TEA, methyl-phenylpyridinium	[46]
hOCTN1	Human fetal liver	551	Apical	TEA	[48]
hOCTN2	Human placenta, kidney	557	Apical	TEA, methylphenylpyridinium	[49, 50]

activity supports this exchange by maintaining the intracellular concentration of dicarboxylate (α-ketoglutarate) to facilitate anion exchange. Thus, cellular entry is uphill against an electrochemical gradient, in turn maintained by the Na^+,K^+-ATPase [2, 24], and inhibition of this enzyme inhibits organic anion accumulation [25–27]. Within the cell, organic anions can be bound or sequestered within vesicles and are extruded across the luminal membrane into tubular fluid by anion exchange or facilitated diffusion [2, 24]. A family of organic anion transporters (OATs) from human, rat, mouse, and flounder [28–32] has recently been identified (Table 1). These transporters are expressed in various tissues, including kidney, liver, and brain, but major interest has focused on OAT1, which is strongly expressed in kidney but only weakly or not at all in other tissues [28, 30, 33]. Human OAT1 maps to chromosome 11 and encodes a 563 amino acid protein with 12 predicted membrane-spanning regions [28, 34]. In the kidney, it is localized to the basolateral surface of proximal tubule cells [28, 35]. When expressed in *Xenopus* oocytes or transfected cells, OAT1 exhibits the functional properties identified in earlier studies of proximal tubular function: concentrative uptake of the organic anion PAH, which is enhanced by *trans* dicarboxylic acids such as α-ketoglutarate and glutarate, and inhibited by a variety of *cis*-acting agents, including probenecid, furosemide, indomethacin, and α-ketoglutarate [28–30, 32–34]. This transporter also has affinity for the nucleoside phosphonates cidofovir and adefovir, antiviral agents that are nephrotoxic [36]. It is not clear whether urate is a substrate for OAT1: ^{14}C-urate uptake occurred in oocytes expressing rat OAT1 [30]. Urate inhibited PAH uptake by oocytes injected with human OAT1 mRNA [28], but urate had no effect on PAH uptake by oocytes expressing rat OAT1 in another study [29]. The basis for these divergent results has not been established. Differences in some features of the protein such as its size [28, 34] suggest that other forms of OAT1 may exist. A human OAT3 has been identified by homology cloning and also maps to chromosome 11 [34]. It has 43% homology to human OAT1, but its substrates have not yet been characterized. Also identified in rat kidney are two other transporters, OAT-K1 and OAT-K2, with somewhat different molecular features and transport properties than OAT1; they appear localized to apical rather than basolateral membranes of cells in the S3 segment of the proximal tubule and have been classified as members of the oatp family [37–40].

These advances in the understanding of organic anion transport have been paralleled by the cloning of a group of organic cation transporters (OCTs), which mediate transport of a variety of organic cations (Table 1) [41, 42]. These bear some homology to OATs with respect to size, amino acid composition, and membrane topology [29, 31, 42]. Four OCTs have been cloned to date. OCT1 has been identified in rat, rabbit, and human and is expressed chiefly in liver, with lower levels of expression in kidney and intestine. An alternatively spliced variant, OCT1A, has been identified in kidney, liver, and intestine [43]. Human OCT1 is polyspecific, with uptake of the organic cation TEA being inhibited by a variety of compounds, including clonidine, quinine, and verapamil [44]. Differences between hOCT1 and rOCT1 occur in both tissue distribution and substrate characteristics [41, 42]. OCT2 is expressed primarily in kidney and brain, but renal expression predominates. Within the kidney,

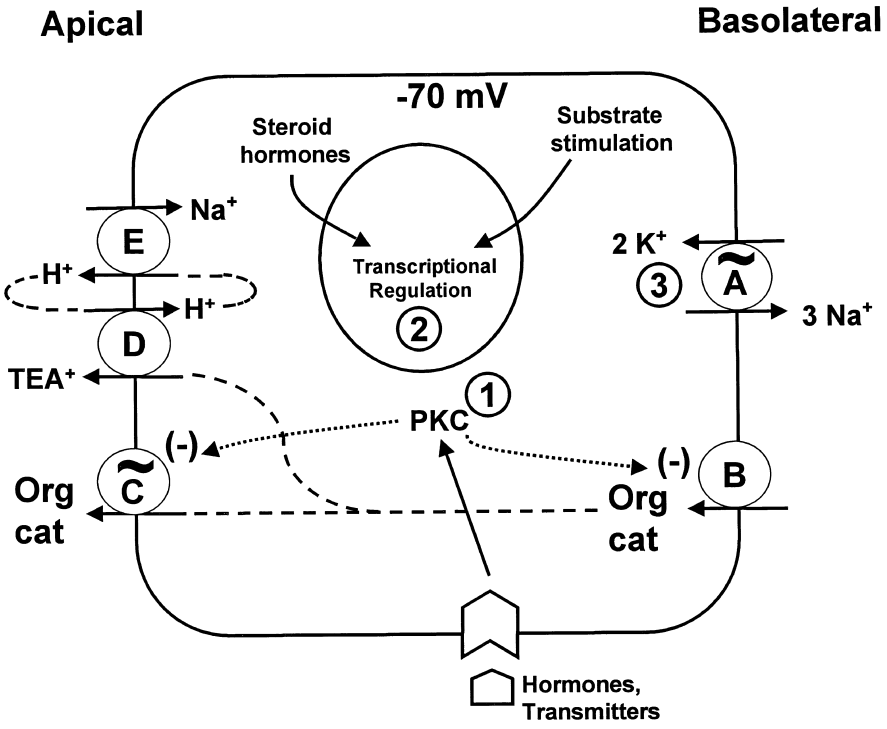

Fig. 2. Schematic diagram of organic cation transport by renal tubular epithelial cells and its regulation. Symbols are the same as described in Figure 1. The electrochemical gradient for Na^+ is maintained by the Na^+,-K^+-ATPase (A). Organic cations (Org cat) enter the cell by facilitated diffusion down the electrical gradient (B) or by simple diffusion and are then taken up into cytoplasmic vesicles (data not shown) or diffuse to the apical membrane. Transfer into tubular fluid occurs via P-glycoprotein electrogenic secretion for larger molecules (C) or by hydrogen-cation exchange (D), which is, in turn, linked to the Na^+-H^+ antiporter (E), for smaller molecules such as tetraethylammonium (TEA^+). As with organic anion transport, regulation occurs via PKC inhibition of P-glycoprotein and OCTs (1), and alterations in nuclear transcription (2). Inhibition of Na^+,K^+-ATPase activity (3) inhibits organic cation entry into the cell by reducing the transmembrane potential difference and reduces secretion across the apical membrane by reducing Na^+-H^+ exchange (discussed in the text). Modified with permission from PRITCHARD JB: Renal handling of organic acids and bases, in *Textbook of Nephrology* (4th ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Lippincott Williams and Wilkins (in press).

transcripts are more abundant in medulla than cortex [45]; immunocytochemical studies place the protein on the apical border of the distal tubule [46]. The concept of multiple OCTs is further supported by the characterization of an organic cation efflux pathway in opossum kidney cells, which is sensitive to some nucleosides [47]. Transport of organic cations is thought to proceed via these transporters down an electrical gradient into the cell across the basolateral membrane and is therefore potential-dependent. Compartmentalization within the cell can occur as is true for organic anions, and a variety of extrusion steps across the brush border into the tubular fluid and uptake back into the cell has been described (Fig. 2) [24, 41, 42]. Some of these may include the other two cloned cation transporters, OCTN1 and OCTN2 [48–50]. These transporters are located on the apical membrane and exhibit pH-dependent transport consistent with a proton-cation antiporter [51]. In addition, OCTN2 also displays sodium-dependent carnitine transport [52, 53]; this is unique among transporters to have two separate mechanisms of organic compound translocation in the same molecule. Human OCTN1 and OCTN2 share 77% amino acid homology [49], but homology with OCT1 and OCT2 is 31 to 37% [48, 49].

Little is known about cellular events regulating organic anion and cation transport in the proximal tubule. Inhibition of sodium transport by agents such as ouabain [54] or vanadate [25–27], which inhibit the Na^+,K^+-ATPase, disrupt the out $>$ in sodium gradient and the driving force for cellular uptake. To the extent that these treatments depolarize the cell, potential-dependent uptake will also be reduced. Considerable evidence indicates that protein kinase C (PKC) can be an important regulator of organic ion transport. Both OATs and OCTs possess several PKC phosphorylation sites [28–30, 39, 41–43, 55], and experimental studies indicate that activation of PKC, by cAMP or with phorbol esters, inhibits uptake of compounds like PAH and TEA [33, 56–59]. Transepithelial transport of the organic anion fluorescein by perfused rabbit tubules is also inhibited by phorbol ester; this inhibition was blocked by the PKC inhibitors staurosporine and bisindolylmaleimide [60]. Some studies link this effect of PKC activation to inhibition of entry into the cell across the basolateral membrane [56–58, 61], whereas another study has suggested that it could be mediated by PKC inhibition of Na^+,K^+-ATPase in the tubular cell, since transport was also inhibited by dopamine and stimulated by oxymetazoline [62]. Against this view of PKC activation inhibiting cellular uptake of organic ions are studies indicating that phorbol esters actually stimulate uptake of TEA and PAH across the basolateral membrane of rabbit proximal tubular cells [63, 64]. The PKC inhibitor staurosporine lowered transport of organic compounds and prevented the stimulation of transport caused by phorbol esters [64]. At present, there is no obvious way to reconcile these divergent observations. It may be that the effects of PKC on tubular secretion reflect different actions of the enzyme on

Na^+,K^+-ATPase or on the transporters depending on oxygen availability and presumably the metabolic state of the tissue [62]. The bulk of evidence indicates that PKC activation inhibits the transepithelial transport of organic compounds via an effect on basolateral transporters to reduce cellular uptake (Figs. 1 and 2). Since PKC is activated by numerous neural and humoral pathways, it seems likely that it represents a major intracellular regulatory mechanism for organic ion transport. It should also be noted that P-glycoprotein and Mrp2 also possess numerous phosphorylation sites [9, 10]. PKC regulation of P-glycoprotein–mediated secretion of xenobiotics has been demonstrated recently in a manner suggesting an inverse relationship between PKC activity and P-glycoprotein-mediated transport [65], much as has also been suggested for organic anion transport (Fig. 1) [58]. Additionally, a recent study indicates that endothelins inhibit ATP-mediated organic compound secretion via P-glycoprotein and Mrp2 in killifish proximal tubules [22]. This action of endothelins was mediated by the ET_B receptor and likely involved activation of PKC, since inhibitors of the enzyme blocked the decrease in tubular secretion [22]. This study underscores the importance of neural and humoral agents that regulate tubular transport of organic compounds via effects on PKC activity.

Some data indicate an interaction of nonsteroidal antiinflammatory drugs (NSAIDs) with anion transport. Although indomethacin *cis* inhibits PAH transport by OAT1, most likely through competition for transport [28, 30, 33], one study observed that NSAIDs inhibited methotrexate transport by OAT-K1 but were not transported themselves [66]. This opens the possibility that inhibition of prostaglandin synthesis by NSAIDs may inhibit some OATs. An effect of albumin to stimulate transcellular transport of organic compounds has been hypothesized, although the mechanism by which this effect occurs has not been defined [67, 68].

In summary, the mechanisms involved in the regulation of tubular secretion of xenobiotics at the cellular level include the activity of Na^+,K^+-ATPase, which indirectly influences cellular uptake by maintaining the sodium gradient and transmembrane potential, PKC activity, which inhibits the transporters, expression of P-glycoprotein, Mrp2, OAT1, and other transporters, the protein binding of substrates, and other factors (Figs. 1 and 2). Further study of the regulation of transporter function will no doubt reveal new mechanisms that could be important in understanding the body's defense against xenobiotics.

Neural and hormonal control

A role of renal efferent nerves in the regulation of tubular secretion has been identified in studies utilizing renal denervation or electrical stimulation of the renal nerves. Renal excretion of PAH in the dog is decreased after renal denervation [69]. Denervation does not prevent the compensatory increase in tubular secretion following unilateral nephrectomy [70], indicating that the mechanism of this increase is not neurally mediated but is perhaps due to humoral or hemodynamic factors. Electrical stimulation of renal efferent nerves leads to an increase in the maximal transport of diodrast [71]. Studies of the effects of increases (efferent nerve stimulation) or decreases (denervation) in renal nerve activity on tubular transport are in some ways at odds with pharmacologic studies. Among adrenergic agents, no direct effect on tubular secretion was observed in dogs or rats after intravenous infusion of norepinephrine, isoproterenol [72], or dopamine [73]. Diodrast transport changed only when the glomerular filtration rate changed simultaneously. This lack of effect could be related to the complex hemodynamic changes that occur during intravenous infusion of these agents. In contrast are the results obtained using membrane vesicles from renal tubular cells. Epinephrine and norepinephrine enhanced PAH transport into basolateral membrane vesicles prepared from rat proximal tubules [74]. The effect was mediated by adrenoreceptors. Clonidine, an α_2-adrenergic agonist, also produced an elevation of uptake into these vesicles [74]. These results were confirmed in a study of dichlorophenoxyacetic acid transport in primary cultures of winter flounder proximal tubule cells. The α-adrenergic agonist oxymetazoline stimulated, and dopamine inhibited, secretion of this organic anion [62]. Acetylcholine did not change the maximum secretion of PAH [75] or diodrast [76] after infusion into the renal artery in dogs, despite the renal vasodilation that likely occurred. This suggests that renal nerve effects are also not solely due to hemodynamic changes. This conclusion is further supported by studies in isolated segments of rabbit proximal tubule in which the α-adrenergic agonist phenylephrine inhibited organic anion transport via a PKC-mediated mechanism [60, 61].

Older studies demonstrate the importance of endocrine glands, particularly anterior pituitary, thyroid, and gonads, in the regulation of tubular secretion. Hypophysectomy decreases the tubular transport of PAH in vivo and in vitro [77, 78]. This effect may reflect deficiency of growth hormone because administration of growth hormone increased tubular transport in both hypophysectomized and intact animals [77]. Tubular transport of organic substances is also reduced after thyroidectomy and is restored by thyroxine therapy [77]. The effect of thyroid hormones on tubular secretion may be age-related. Hirsch and Hook found that administration of triiodothyronine (T_3) to weanling rats for three or seven days caused an increase in PAH transport in renal cortical slices while treatment of adult rats did not alter transport significantly [79]. When added to renal slices in vitro, T_3 inhibited PAH uptake. This confirmed the earlier observation concerning thyroxine action in vitro [80] and

was considered to be the result of competition with PAH, since the hormone is transported as an organic anion [79]. Subsequent studies demonstrated that thyroid hormones increased tubular secretion in adult rats and rabbits without a change in glomerular filtration rate (GFR). Aurantin, which blocks the synthesis of mRNA and protein, prevented the stimulation of secretion by thyroid hormones [81, 82], suggesting that an effect on gene transcription likely occurs in addition to any competition for transport. Bräunlich confirmed the increase in tubular secretion by thyroid hormones administered to rats of different ages [83, 84]; the effect was associated with an increase in protein synthesis in kidney tissue [85]. Recently, stimulation of PAH secretion by T_3 has also been observed in frog kidneys [86]. These studies are consistent with earlier organ ablation experiments demonstrating that thyroidectomy reduced tubular transport of organic substances [77].

Parathyroid hormone and its intracellular second messenger cAMP (10^{-4} mol/L) both increase PAH uptake by suspensions of rabbit renal cortical tubules. A higher concentration of cAMP (10^{-3} mol/L) inhibits PAH uptake, probably by a competitive mechanism [87]. The data do not agree regarding the effect of increased intracellular cAMP caused by isoproterenol or theophylline on PAH transport [88]. Parathyroid hormone-mediated inhibition of PAH transport in opossum kidney epithelial cells [56] was attributed to activation of PKC [56, 57]; the role of PKC on tubular secretion has been discussed previously in this article. Insulin effects on organic ion transport have also been observed. Intravenous injection in dogs increased the T_m of diodrast while urine flow and excretion of sodium and potassium diminished without change in GFR [89]. Similarly, infusion of insulin into a renal artery was accompanied by a unilateral increase in tubular secretion and decrease in urinary sodium and potassium excretion. In rabbits, insulin stimulated the accumulation of diodrast by renal cortical slices whether the hormone was injected into the animals or added to the incubation medium of the slices [89]. The mechanism of this effect of insulin on organic ion transport has not been established.

Steroid hormones have also been shown to influence organic ion transport. Single injections of hydrocortisone (cortisol) increase diodrast excretion in dogs and rabbits and cause an increase in uptake of this compound by rabbit renal cortical slices. However, prolonged administration of hydrocortisone has the opposite effect [90]. Prednisolone and dexamethasone increase the excretion of PAH and its accumulation by renal slices in immature but not in adult rats, while triamcinolone is effective regardless of age [91]. The administration of testosterone increases the accumulation of PAH by renal slices from female but not male rats [92]. This stimulatory effect of testosterone on tubular secretion in female rats and gonadectomized male rats can be prevented by aurantin [93] and is therefore likely due to enhanced synthesis of RNA and proteins. Related to these observations are others demonstrating sex-related differences in tubular transport. Renal cortical slices from male rats accumulate PAH to a greater extent than those from female rats [92, 94–96]. This is also true regarding the organic cation TEA [96]. Castration of male rats causes a reduction in tubular secretion, which is corrected by treatment with testosterone, while bilateral ovariectomy does not alter tubular secretion in female rats [92, 94, 95]. Testosterone treatment increases the number of functional carriers for PAH in the kidney [97]. However, some xenobiotics are transported better by female animals; among these are perfluorooctanoic acid [98], pentachloronitrobenzene [99], zenarestat [100], and nilvadipine [101]. Species differences also exist: The sex difference in the excretion of zenarestat is seen in mice and rats, but not in dogs or humans [102]. It must be born in mind that the clearance methods used in these studies have limitations, and other factors, including transport by the liver, may play a role in the excretion of these drugs. More direct methods, such as determination of maximum transport (T_m), or experiments in vitro, are necessary to clarify underlying mechanisms. Although the data on tubular effects of estrogens are not clear at present, these observations in aggregate suggest important differences in tubular secretion related to the sex steroids, with testosterone being a potent stimulator of transport and estrogen having a lesser effect.

This summary leads to the conclusion that hormonal influences on tubular secretion of organic compounds take place through at least two pathways (Figs. 1 and 2). One involves regulation through a cytoplasmic action(s), likely mediated by PKC and perhaps other mechanisms. This pathway may be the one used by hormones and transmitters interacting with receptors on the surface of the tubular epithelial cell. The other occurs through effects on nuclear transcription and may involve synthesis of new transporters and substrates important in tubular secretion. This pathway is likely the one by which steroid hormones and perhaps other regulators act. Future research will expand information on these regulatory pathways and no doubt uncover other ones by which regulation of tubular secretion occurs.

Substrate stimulation

Hirsch and Hook were the first to demonstrate that prior injection of penicillin (twice daily for 3 days) to rabbit pups two weeks old led to an increase in the uptake of PAH by kidney cortical slices [103–105]. The effect was shown in only immature rabbits or rats and was not present after four weeks of age when tubular secretion reached the adult level. This increase in anion uptake was not paralleled by an increase in the uptake

of the organic cation N-methylnicotinamide. When pregnant rabbits were treated with penicillin during the last half of pregnancy, PAH transport was increased in renal slices from the newborns in the first days of life. Substrate stimulation of organic anion transport in renal slices was confirmed later in newborn dogs [106]. This phenomenon is considered to be a result of increased biosynthesis of transport proteins, since pretreatment with penicillin leads to greater incorporation of leucine and glutamine into the slice proteins and to enhancement of protein content in the microsomal fraction, whereas administration of the protein synthesis inhibitor cycloheximide to nursing rats prevents substrate stimulation of PAH uptake by renal slices [107]. In addition to these studies on renal cortical slices, substrate stimulation of tubular secretion has been demonstrated using separated renal tubules from newborn rabbits [108] and also in in vivo experiments in newborn dogs [109].

Several reports have described substrate stimulation of tubular secretion not only in newborn but also in adult animals [110, 111]. Repeated administration of phenol red, penicillin, cyclopenthiazide, and other substrates led to an increase of renal excretion of PAH regardless of age [112]. Pretreatment with penicillin and diodrast stimulates their tubular secretion by adult rat kidneys, while inhibitors of protein synthesis, puromycin, and cycloheximide prevent this effect [113]. The ability of cycloheximide to prevent substrate stimulation has been confirmed using renal slices from adult rats [114]. In aggregate, the data from these [107, 113, 114] and other studies argue that substrate stimulation occurs as a result of increased synthesis of protein transporters involved in the secretion of the organic compounds. The most convincing results concerning substrate stimulation of tubular secretion in vivo have been obtained from determination of the T_m of penicillin or diodrast in conscious dogs in control experiments and again after three days of administration of the substrates three times daily [115]. A significant increase in maximum transport of both compounds was observed, while glomerular filtration was unchanged.

The reason that substrate stimulation of tubular secretion has been demonstrated in only immature animals by some investigators but also in adults by others is not known for certain, but may depend on the time after preliminary substrate administration that transport is measured. If penicillin or diodrast is injected into adult animals three times daily for three days, substrate stimulation can be shown up to 18 hours after the last injection [113]. Since tubular secretion in newborn animals is very low, the duration of substrate stimulation may be prolonged up to 24 hours after the last injection or even later, whereas in adult animals the stimulation does not last as long. It should be pointed out that the number of preliminary injections of substrate is not critical for stimulation of tubular secretion, since the phenomenon has been observed not only after repeated injections of substrates three times daily for three days, but also after administration of the substrate only twice during one day [116].

Varshavsky has reported unique data concerning the dynamics of tubular secretion during continuous intravenous infusion of diodrast and inulin in rats and dogs [117]. In these experiments, T_m of diodrast was estimated every 5 to 10 minutes for 2 hours, during which time three levels of T_m were identified: the first from 5 to 25 minutes (the background), the second from 35 to 55 minutes, and the third from 65 to 120 minutes. T_m in the second period had increased to 136 to 139% of background and in the third period to 178 to 181%, where it remained stable. Thus, substrate stimulation of tubular secretion appears to be a gradually incremental process. Finally, [^{14}C]TEA transport by opossum kidney cells is enhanced after exposure to organic cations such as choline or N-methylnicotinamide [abstract; Chan and Giacomini, *Pharm Res* 10(Suppl):S411, 1993], suggesting that substrate stimulation of cation transport may also occur.

Morphological correlates of substrate stimulation have been variably observed. No histologic changes in renal cortical slices from penicillin-induced PAH accumulation in immature rabbits were noted [118], nor were ultrastructural changes seen in proximal tubules of two-week-old rabbits receiving penicillin twice daily for 2 days and sacrificed 24 hours after the final injection [119]. However, another group detected some morphological changes in rats after substrate stimulation with diodrast injections administered three times a day [120, 121]. Renal cortical slices made four hours after the final injection showed increases in the number of ribosomes and in the diameter of microcisterns in the endoplasmic reticulum in proximal tubular cells, as well as an increase in the number and size of microbodies [120, 121]. The significance of these ultrastructural changes is not known.

PHARMACOLOGICAL ASPECTS

Nervous system agents

Older reports examined the effect of hypnotics on tubular secretion. Despopoulos investigated the effect of barbiturates on the accumulation of PAH by rabbit kidney cortex slices [122]. Most of them, including barbital, phenobarbital, and hexobarbital, decreased transport without a reduction in oxygen utilization. They did not alter the transport of the organic cation TEA, indicating a specific effect on organic anion transport. On the other hand, amobarbital and secobarbital decreased oxygen consumption and the transport of both PAH and TEA, suggesting a more global effect on transport. Pentobarbital injected intravenously reduced the maximum transport of PAH in dogs [123, 124] and decreased the uptake

of PAH and oxygen consumption by rat kidney slices [125]. Hexobarbital, whether given by intravenous injection to rabbits or by infusion into the left renal artery to dogs, reduced the tubular secretion of diodrast; in the latter case, tubular secretion in the right kidney remained unchanged [126]. These studies indicate that barbiturates inhibit tubular secretion by a direct influence on tubule cells, either by altering metabolism or by a competitive interaction with the transporters. The administration of the central nervous stimulants strychnine or amphetamine failed to change renal tubular secretion in rabbits and dogs [126].

It has recently been shown that ethanol (10 to 40 mmol/L) stimulates uptake of the organic anion fluorescein in proximal tubules of rat renal slices, an effect that was abolished by inhibition of ethanol oxidation [127]. This observation was interpreted to indicate that the increase of tubular transport by ethanol is mediated by the production of acetate, well known as a stimulant of tubular secretion [1, 2].

Cardiac glycosides

Several reports indicate that PAH accumulation by rat or rabbit renal cortical slices [54, 128, 129] or primary cultures of winter flounder proximal tubule cells [130] is reduced if the medium contains cardiac glycosides. In vivo, infusion of strophanthin (ouabain) into the renal artery of dogs at 10 μg/min led to an initial small but significant increase in maximum transport of diodrast in the infused kidney, followed by a decrease as sodium excretion increased [131]. At an infusion rate of 25 μg/min, tubular secretion decreased without the initial rise, the maximum reduction of diodrast transport coinciding with the time of maximum natriuresis. These results were later confirmed in vitro by studying the influence of ouabain on organic anion transport in rabbit renal slices [132]. At an ouabain concentration of 10^{-5} to 10^{-4} mol/L, inhibition of PAH transport took place, but lower concentrations (10^{-7} to 10^{-6} mol/L) stimulated PAH transport. This dual effect of ouabain was attributed to changes in intracellular sodium and potassium concentrations, since lower concentrations of ouabain ($<10^{-6}$ mol/L) did not change intracellular cation content [132]. The importance of Na^+,K^+-ATPase for tubular secretion is also indicated by the effect of a potent inhibitor of this enzyme, vanadate, that markedly decreased PAH and TEA accumulation by rat renal cortical slices [25, 26] and PAH secretion in isolated rabbit proximal tubules [27]. The importance of the sodium gradient in energizing organic ion transport was discussed previously in this article. Inhibition of the Na^+,K^+-ATPase disrupts this gradient and thereby inhibits tubular secretion indirectly rather than by a direct action on the transporters themselves.

Diuretics

The effect of mercurial diuretics on tubular secretion has been reviewed [133]. As to modern diuretics, single doses of hydrochlorothiazide and cyclopenthiazide did not change tubular secretion in rats, whereas daily administration of hydrochlorothiazide (20 mg/kg to rats and 5 mg/kg to dogs for 10 days) and cyclopenthiazide (50 mg/kg to rats) led to a gradual increase in the tubular secretion of diodrast [134, 135]. The authors suggested that these results reflected substrate stimulation of tubular transport. Furosemide reduced the secretion of penicillin in rats [136] and the accumulation of PAH by isolated S2 segments of rat proximal tubules [137]. The results may be due to competition, since furosemide is secreted by the organic anion transport system. Bresler and Natochin demonstrated that furosemide, ethacrynic acid, triamterene, and other diuretics in doses inhibiting sodium reabsorption reduced the transport of fluorescein through the luminal membrane of frog proximal tubules [138]. Single subcutaneous injections of furosemide in therapeutic doses did not affect the tubular secretion of diodrast in rats and dogs [139]. The explanation of diuretic effects on tubular secretion is complex in view of the competitive interaction with other secreted substances on the one hand and the ability for substrate stimulation on the other. It seems likely that therapeutic doses of modern diuretics do not change tubular secretion significantly.

Protein synthesis stimulants and inhibitors

Since testosterone stimulates tubular secretion by enhancing protein synthesis, as discussed previously in this article, it has been of interest to study the effect of synthetic anabolic steroids. The administration of nandrolone decanoate for seven days to dogs and rats caused a pronounced increase in renal diodrast secretion, which was accompanied by a rise in protein content in the microsomal fraction of renal cortical cell homogenates [140]. Similar results were obtained using another anabolic agent, potassium orotate. Daily administration of this compound for 7 days to rats and 10 days to dogs led to a marked increase in tubular secretion of diodrast as well as to an increase in protein synthesis in the renal cortex [141]. Two different inhibitors of protein synthesis, cycloheximide and aurantin, effectively blocked the ability of potassium orotate to stimulate the tubular transport of xenobiotics [141]. Thus, agents that stimulate protein synthesis lead to an increase in the transport of organic compounds, while inhibitors of protein synthesis produce the opposite effect. It is to be presumed that these effects are mediated by stimulation or inhibition of the synthesis of transport proteins such as OAT1 and OCT1 themselves.

Microsomal enzyme inducers have long been known

to stimulate hepatic drug metabolism, but little has been reported about their effects on the renal transport of xenobiotics despite the presence in the proximal tubule of the cytochrome P450-monooxygenase system. The administration of the classical microsomal inducers, phenobarbital and 3-methylcholanthrene increased PAH uptake by renal cortical slices from immature rabbits [142]. Also, the administration of phenobarbital (50 mg/kg, 4 days) and 3-methylcholanthrene (20 mg/kg, 2 days) to rats was accompanied by a large increase in excretion and maximum transport of diodrast without change in urine flow or increase in glomerular filtration rate [143]. Another inducer of the monooxygenase system, zixorin, stimulated the tubular secretion of diodrast when administered to rats (100 mg/kg, 4 days), and this effect lasted for a few days after the end of the treatment [144]. The mechanism of the increase in tubular secretion by microsomal enzyme inducers is not clear yet. It could be secondary to stimulation of biotransformation processes or to enhancement of tubular transport system activity.

Injection of aurantin, an inhibitor of protein synthesis related to actinomycin D (0.1 mg/kg subcutaneously daily for 3 or 4 days) to rats, led to a small increase in diodrast secretion on the second day and to a more considerable decrease of secretion in the four to eight days after starting the injections [145]. Renal cortical slices of treated rats accumulated diodrast less efficiently (S/M = 3.8 ± 0.34 compared with 5.7 ± 0.35 in control). When aurantin was added to the slice medium at a concentration of 0.01 mg/mL, the S/M ratio increased a small amount; when the concentration was higher (0.02 mg/mL), the S/M ratio decreased. Intravenous injection of aurantin (0.125 mg/kg) in dogs decreased the maximum transport of diodrast significantly. The changes in tubular secretion in rats correlated with the protein content in renal cortical tissue. RNA content was reduced simultaneously with the decrease in secretion [145], suggesting a global effect of the drug on gene transcription and subsequent protein synthesis.

Some antibiotics that inhibit protein synthesis also reduce tubular transport of organic compounds. Tetracycline, oxytetracycline, and chlortetracycline, when administered to dogs (150 mg/kg daily for 10 days), inhibit tubular secretion; chloramphenicol causes the same effect by single and repeated administration in rats [133]. The aminoglycoside antibiotics neomycin and monomycin decrease tubular secretion, whereas kanamycin in low doses improves tubular transport [133]. Aminoglycoside nephrotoxicity is associated not only with inhibition of ribosomal protein synthesis, but also in part with an alteration in the expression of genes critical for proximal tubule metabolism and maintenance of basolateral transport [146]. In rats treated with gentamicin, Na^+,K^+-ATPase activity in tubule cells is reduced [147], an effect that will decrease organic ion transport indirectly by disrupting the sodium gradient, as discussed earlier.

Cytostatic (antineoplastic) agents

Antineoplastic drugs and x-irradiation also have effects on renal tubular transport of xenobiotics by inhibiting synthesis of nucleic acids and proteins in tubular transport systems. Administration of 6-mercaptopurine for 10 days to rabbits and dogs causes a dose-dependent depression of tubular secretion of diodrast; uptake of diodrast by rabbit renal cortical slices is also decreased [148]. A single intravenous injection of cyclophosphamide in rabbits (60 to 80 mg/kg) and dogs (40 mg/kg) leads to a marked inhibition of diodrast excretion, an effect accompanied by reduced accumulation of the xenobiotic by renal slices [149]. It is of interest that addition of cyclophosphamide directly to the slice incubation medium had no effect on active transport, but if the compound was injected into rabbits, the accumulation of diodrast was reduced considerably [149]. This conforms to the view that cyclophosphamide must be activated in the body in order to liberate an effective alkylating derivative.

The wide application of cisplatin as an antineoplastic agent is limited by its nephrotoxicity. In experiments in rats, cisplatin impairs the ability of renal slices to accumulate both PAH and TEA for some days after the injection [150, 151]; the addition of cisplatin to the incubation medium reduced the accumulation of these organic compounds in a dose-dependent manner [152, 153]. Sulfofluorescein accumulation by cortical tissue is also reduced [150]. The nephrotoxicity of cisplatin is probably linked to its tubular secretion by both anion and cation transport systems and to its ability to depress renal metabolism, including Na^+,K^+-ATPase activity [154]. Thus, its effects to decrease transport of organic compounds are probably both direct and indirect.

Whole-body irradiation causes depression of tubular secretion, but it is not clear whether the effect is due to a direct action on renal tissue. Local single-dose x-irradiation of dog kidneys with 2400 R did not cause a marked change in PAH transport [155]. However, Brukhanov observed a reduction of tubular secretion not only with whole-body irradiation of rabbits but also after local x-irradiation of the kidney area with a dose of 86 R/minutes over 30 minutes (total dose 2580 R) [156]. Glomerular filtration rate and urine flow did not change significantly.

Immunomodulators

As has been described previously in this article, some drugs with immunosuppressive activity, including cytostatic agents and high doses of hydrocortisone decrease tubular secretion. CsA is a widely used potent immunosuppressive drug that selectively inhibits T lymphocytes. The influence of CsA on tubular secretion is difficult to

study since it markedly reduces renal blood flow. It has been shown, using a kidney epithelial cell line and the isolated perfused rat kidney, that CsA inhibits the tubular secretion of digoxin [19], while on the other hand, digoxin does not affect CsA transport. The authors interpreted this effect of CsA as due to modification of the multidrug transporter P-glycoprotein in tubular cells, as discussed earlier. It is also possible that inhibition of the tubular secretory system by CsA may be related to its ability to suppress renal microsomal protein synthesis [157] or to inhibition of PKC [158]. This latter is speculative since, as discussed previously in this article, the bulk of evidence indicates that PKC activation rather than inhibition inhibits transport of organic compounds.

Only a few reports have studied the effects of immunostimulants on tubular transport. The bacterial lipopolysaccharide prodigiosan (0.05 mg/kg) and the synthetic compound levamisole (10 mg/kg) injected subcutaneously to rats three times every other day caused an increase in tubular secretion and excretion of diodrast; the increase in diodrast excretion by prodigiosan was 21% and by levamisole 28%. Transport returned to baseline one week after the end of treatment [159]. Since levamisole is an immunomodulator and its effect depends on the dose, a larger dose of the drug (50 mg/kg) with no immunostimulant action was tested. Under these circumstances, tubular secretion remained unchanged [159]. Thus levamisole activates the tubular transport of xenobiotics only in an immunostimulating dose (10 mg/kg). Another immunostimulant, 5-oxymethyluracil (50 mg/kg daily for 7 days), also increased tubular secretion in rats. The maximum transport of diodrast was 36% higher than basal, while glomerular filtration did not change [160]. A number of compounds with immunologic activity have been obtained from the thymus. One of these is Tactivin (or T-activin). Administered to rats, Tactivin increased maximum tubular transport of diodrast on average by 73% without change in glomerular filtration, an effect that returned to control levels six days after the end of Tactivin injections [161]. The mechanism of stimulation of tubular transport by these immunostimulants is not known, but it is attractive to speculate that it could occur through an increase in tubular cell protein synthesis.

Miscellaneous

There are several old reports about the reduction of tubular secretion in dogs and rats caused by salicylates as well as after prolonged administration of aminopyrine, phenylbutazone, and acetaminophen, whereas vitamin A has been shown to stimulate the tubular transport of xenobiotics [reviewed in 133]. Folic acid has also been shown to stimulate renal PAH transport [162]. Among more recent reports, attention has been paid to agents that induce lipid peroxidation; they decrease PAH accumulation by rat renal cortical slices significantly, while the addition of an antioxidant inhibits the peroxidation and restores the accumulation of PAH [163].

CONCLUSION

A few years ago, Pritchard and Miller noted the importance of studying the regulation of tubular secretion [24]. This review has attempted to summarize currently available information on this subject. The regulation of tubular transport is best viewed using an integrated approach [164], taking into account the interaction between renal and hepatic excretion [165–168] as well as the role of renal cell organelles in the compartmentalization and transcellular transport of organic substances [2, 121, 169]. Xenobiotics are generally recognized as an important cause of human diseases, including chemical allergies, diverse immunodeficiencies, and malignant tumors. It is now accepted that preservation of overall homeostasis occurs through the operation of different mechanisms. One of these is the immune system, which deals with macromolecular xenobiotics, mainly foreign proteins. Another involves the liver, which excretes some xenobiotics into bile and hydroxylates or conjugates others. The third is the system of secretion by the renal proximal tubules. Tubular secretion, which evolved during the early steps of phylogenesis, allows for excretion of foreign low molecular weight compounds or excess amounts of endogenous substances, providing protection for the organism from potential toxicities. These pathways for defense against foreign substances may be interrelated: protein synthesis inhibitors such as cycloheximide, aurantin, and tetracyclines, and immunosuppressants like CsA, x-irradiation, large doses of cortisol, 6-mercaptopurine, cyclophosphamide, and cisplatin all suppress tubular transport of xenobiotics as well as inhibit the immune response, while immune stimulants like prodigiosan, tactivin and levamisol, and agents, which stimulate protein synthesis like anabolic steroids and thyroid hormones, enhance tubular secretion. In many cases, it is not yet possible to determine whether regulation of transport of organic compounds occurs via a direct effect on the transporters themselves or through indirect actions such as alterations in cell metabolism or changes in the sodium gradient. Future research is necessary to clarify this important issue. Substrate stimulation of tubular secretion has the obvious benefit of accelerating removal of a potentially toxic compound to which the body may be exposed repetitively. Given the increasing number of xenobiotics introduced into our environment, tubular secretion is a critical body function, and further study of its regulation and its interaction with other protective systems should reveal novel ways by which protection could be enhanced. The identification of the molecular pathways and transporters involved in tubular secretion will facilitate this effort.

NOTE ADDED IN PROOF

Two reviews of the tubular transport of organic compounds have appeared since the submission of this article: Burckhardt G, Wolff NA: Structure of renal organic anion and cation transporters. *Am J Physiol* 278: F853–F866, 2000; and Inui K-I, Masuda S, Saito H: Cellular and molecular aspects of drug transport in the kidney. *Kidney Int* 58:944–958, 2000

ACKNOWLEDGMENTS

We are grateful to Drs. V. Kvitash and M. Mendelson for their advice and help in the preparation of this manuscript.

Reprint requests Michael H. Humphreys, M.D., Box 1341, SFGH, University of California San Francisco, San Francisco, California 94143, USA.
E-mail: mhhsfgh@itsa.ucsf.edu

REFERENCES

1. Roch-Ramel F, Besseghir K, Murer H: Renal excretion and tubular transport of organic anions and cations, in *Handbook of Physiology (Sect 8 Renal Physiology)*, edited by Windhager EE, Bethesda, Oxford University of Press, 1992, pp 2189–2262
2. Pritchard JB, Miller DS: Mechanisms mediating renal secretion of organic anions and cations. *Physiol Rev* 73:765–796, 1993
3. Sica DA, Schoolwerth AC: Renal handling of organic anions and cations and renal excretion of uric acid, in *The Kidney* (5th ed), edited by Brenner BM, Philadelphia, Saunders Co., 1996, pp 607–626
4. Roch-Ramel F, Diezi J: Renal transport of organic ions and uric acid, in *Diseases of the Kidney* (6th ed), edited by Schrier RW, Gottschalk CW, Boston, Little, Brown, 1997, pp 231–249
5. Ullrich KJ, Rumrich G: Luminal transport step of para-aminohippurate (PAH): Transport from PAH-loaded proximal tubular cells into the tubular lumen of the rat kidney in vivo. *Pflügers Arch* 433:735–743, 1997
6. Bellamy W: P-glycoproteins and multidrug resistance. *Ann Rev Pharmacol* 36:161–183, 1996
7. Stein WD: Kinetics of the multidrug transporter (p-glycoprotein) and its reversal. *Physiol Rev* 77:545–590, 1997
8. Gottesman MM, Pastan I: The multidrug transporter, a double-edged sword. *J Biol Chem* 263:12163–12166, 1988
9. Ambudkar SV, Dey S, Hrycyna CA, *et al*: Biochemical, cellular and pharmacological aspects of the multidrug transporter. *Annu Rev Pharmacol* 39:361–398, 1999
10. Silverman JA: Multidrug-resistance transporters. *Pharm Biotechnol* 12:353–386, 1999
11. Horio M, Chin K-V, Currier SJ, *et al*: Transepithelial transport of drugs by the multidrug transporter in cultured Madin-Darby canine kidney cell epithelia. *J Biol Chem* 264:14880–14884, 1989
12. Tanigavara Y, Okamura N, Hirai M, *et al*: Transport of digoxin by human p-glycoprotein expressed in a porcine kidney epithelial cell line LLC-PK_1. *J Pharmacol Exp Ther* 263:840–885, 1992
13. Ito T, Yano I, Tanaka K, *et al*: Transport of quinolone antibacterial drugs by human p-glycoprotein expressed in a kidney epithelial cell line, LLC-PK_1. *J Pharmacol Exp Ther* 282:955–960, 1997
14. Miller DS, Fricker G, Drewe J: P-Glycoprotein-mediated transport of a fluorescent rapamycin derivative in renal proximal tubule. *J Pharmacol Exp Ther* 282:440–444, 1997
15. Ullrich K, Rumrich G, David C, *et al*: Bisubstrates: Substances that interact with renal contraluminal organic anion and organic cation transport systems. I. Amines, piperidines, piperazines, azepines, pyridines, quinolines, imidazoles, thiazoles, guanidines and hydrazines. *Pflügers Arch* 425:280–299, 1993
16. Ford JM, Hait WN: Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 42:155–199, 1990
17. Twentyman PR: Cyclosporines as drug resistance modifiers. *Biochem Pharmacol* 43:109–117, 1992
18. Delannoy IAM, Mandin RS, Silverman M: Renal secretion of vinblastine, vincristine, and colchicine in vivo. *J Pharmacol Exp Ther* 268:388–395, 1994
19. Okamura N, Hirai M, Tanigawara Y, *et al*: Digoxin-cyclosporin A interaction: Modulation of the multidrug transporter p-glycoprotein in the kidney. *J Pharmacol Exp Ther* 266:1614–1619, 1993
20. Schaub TP, Kartenbeck J, Konig J, *et al*: Expression of the conjugate export pump encoded by the *mrp2* gene in the apical membrane of kidney proximal tubules. *J Am Soc Nephrol* 8:1213–1221, 1997
21. Keppler D, Leier I, Jedlitschky G, *et al*: ATP-dependent transport of glutathione S-conjugates by the multidrug resistance protein MRP1 and its apical isoform MRP2. *Chem Biol Interact* 111–112:153–161, 1998
22. Masereeuw R, Terlouw SA, van Aubel RAMH, *et al*: Endothelin B receptor-mediated regulation of ATP-driven drug secretion in renal proximal tubule. *Mol Pharmacol* 57:59–67, 2000
23. Keppler D, Konig J: Hepatic canalicular membrane 5: Expression and localization of the conjugate export pump encoded by the MRP2 (cMRP/cMOAT) gene in liver. *FASEB J* 11:509–516, 1997
24. Pritchard JB, Miller DS: Renal secretion of organic anions and cations. *Kidney Int* 49:1649–1654, 1996
25. Sheikh MI, Maxild J, Möller JV: Effect of vanadate on the renal accumulation of p-aminohippurate in the rabbit kidney tubule in vitro. *Biochem Pharmacol* 30:2141–2146, 1981
26. Smith JH, Braselton WE, Tonsager SR, *et al*: Effects of vanadate on organic ion accumulation in rat renal cortical slices. *J Pharmacol Exp Ther* 220:540–546, 1982
27. Edwards RM, Grantham JJ: Effect of vanadate on fluid absorption and PAH secretion in isolated proximal tubules. *Am J Physiol* 244:F367–F375, 1983
28. Hosoyamada M, Takashi S, Yoshikatsu K, *et al*: Molecular cloning and functional expression of a multispecific organic anion transporter from human kidney. *Am J Physiol* 276:F122–F128, 1999
29. Sweet DH, Wolff NA, Pritchard JB: Expression cloning and characterization of ROAT1. *J Biol Chem* 272:30088–30095, 1997
30. Sekine T, Watanabe N, Hosoyamada M, *et al*: Expression cloning and G12 characterization of a novel multispecific organic anion transporter. *J Biol Chem* 272:18526–18529, 1997
31. Lopez-Nieto CE, You G, Bush KT, *et al*: Molecular cloning and characterization of NKT, a gene product related to the organic cation transporter family that is almost exclusively expressed in the kidney. *J Biol Chem* 272:6471–6478, 1997
32. Wolff NA, Werner A, Burkhardt S, *et al*: Expression cloning and characterization of a renal organic anion transporter from winter flounder. *FEBS Lett* 417:287–291, 1997
33. Lu R, Chan BS, Schuster VL: Cloning of the human kidney PAH transporter: Narrow substrate specificity and regulation by protein kinase C. *Am J Physiol* 276:F295–F303, 1999
34. Race JE, Grassi SM, Williams WJ, *et al*: Molecular cloning and characterization of two novel human renal organic anion transporters (hOAT1 and hOAT3). *Biochem Biophys Res Commun* 255:08–514, 1999
35. Sweet DH, Miller DS, Pritchard JB: Localization of an organic anion transporter-GFP fusion construct (rROAT1-GFP) in intact proximal tubules. *Am J Physiol* 276:F864–F873, 1999
36. Cihlar T, Lin D, Pritchard JB, *et al*: Antiviral nucleoside phosphonates cidofovir and adefovir are novel substrates for human and rat renal organic anion transporter I. *Mol Pharmacol* 56:570–580, 1999
37. Bergwerk AJ, Shi X, Ford AC, *et al*: Immunologic distribution of an organic anion transport protein in rat liver and kidney. *Am J Physiol* 271:G231–G238, 1996
38. Masuda S, Saito H, Nonguchi H, *et al*: mRNA distribution and membrane localization of the OAT-K1 organic anion transporter in rat renal tubules. *FEBS Lett* 407:127–131, 1997
39. Saito H, Masuda S, Inui K-I: Cloning and functional characterization of a novel rat organic anion transporter mediating basolateral uptake of methotrexate in the kidney. *J Biol Chem* 271:20719–20725, 1996

40. Masuda S, Ibaramoto K, Takeuchi A, *et al*: Cloning and functional characterization of a new multispecific organic anion transporter, OAT-K2, in rat kidney. *Mol Pharmacol* 55:743–752, 1999
41. Zhang L, Brett CM, Giacomini KM: Role of organic cation transporters in drug absorption and elimination. *Annu Rev Pharmacol Toxicol* 38:431–460, 1998
42. Koepsell H, Gorboulev V, Arndt P: Molecular pharmacology of organic cation transporters in kidney. *J Membr Biol* 167:103–117, 1999
43. Zhang L, Dresser MJ, Chun JK, *et al*: Cloning and functional characterization of a rat renal organic cation transporter isoform (rOCT1A). *J Biol Chem* 272:16548–16554, 1997
44. Zhang L, Schaner ME, Giacomini KM: Functional characterization of an organic cation transporter (hOCT1) in a transiently transfected human cell line (HeLa). *J Pharmacol Exp Ther* 286:354–361, 1998
45. Okuda M, Saito H, Urakami Y, *et al*: cDNA cloning and functional expression of a novel rat kidney organic cation transporter, OCT2. *Biochem Biophys Res Commun* 224:500–507, 1996
46. Gorboulev V, Ulzheimer JC, Akhounddova A, *et al*: Cloning and characterization of two human polyspecific organic cation transporters. *DNA Cell Biol* 16:871–881, 1997
47. Chen R, Pan BF, Sakurai M, *et al*: A nucleoside-sensitive organic cation transporter in opossum kidney cells. *Am J Physiol* 276:F323–F328, 1999
48. Tamai I, Yabuuchi H, Nezu J-I, *et al*: Cloning and characterization of a novel human pH-dependent organic cation transporter OCTN1. *FEBS Lett* 419:107–111, 1997
49. Wu X, Prasad PD, Leibach FH, *et al*: cDNA sequence, transport function, and genomic organization of human OCTN2, a new member of the organic cation transporter family. *Biochem Biophys Res Commun* 246:589–595, 1998
50. Tamai I, Ohashi R, Nezu J-I, *et al*: Molecular and functional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2. *J Biol Chem* 273:20378–20382, 1998
51. Yabuuchi H, Tamai I, Nezu J-I, *et al*: Novel membrane transporter OCTN1 mediates multispecific, bidirectional, and pH-dependent transport of organic cations. *J Pharmacol Exp Ther* 289:768–773, 1999
52. Wu X, Juang W, Prasad PD, Seth P, *et al*: Functional characteristics and tissue distribution pattern of organic cation transporter 2 (OCTN2), an organic cation/carnitine transporter. *J Pharmacol Exp Ther* 290:1482–1492, 1999
53. Ohashi R, Tamai I, Yabuuchi H, *et al*: Na^+-dependent carnitine transport by organic cation transporter (OCTN2): Its pharmacological and toxicological relevance. *J Pharmacol Exp Ther* 291:778–784, 1999
54. Villalobos AR, Dunnick CA, Pritchard JB: Mechanism mediating basolateral transport of 2,4-dichlorophenoxyacetic acid in rat kidney. *J Pharmacol Exp Ther* 278:582–589, 1996
55. Terashita S, Dresser MJ, Zhang L, *et al*: Molecular cloning and functional expression of a rabbit renal organic cation transporter. *Biochim Biophys Acta* 1369:1–6, 1998
56. Nagai J, Yano I, Hashimoto Y, *et al*: Inhibition of PAH transport by parathyroid hormone in OK cells: Involvement of protein kinase C pathway. *Am J Physiol* 273:F674–F679, 1997
57. Takano M, Nagai J, Yasuhara M, *et al*: Regulation of p-aminohippurate transport by protein kinase C in OK kidney epithelial cells. *Am J Physiol* 271:F469–F475, 1996
58. Miller DS: Protein kinase C regulation of organic anion transport in renal proximal tubule. *Am J Physiol* 274:F156–F164, 1998
59. Uwai Y, Okuda M, Takami K, *et al*: Functional characterization of the rat multispecific organic anion transporter OAT1 mediating basolateral uptake of anionic drugs in the kidney. *FEBS Lett* 438:321–324, 1998
60. Shuprisha A, Lynch RM, Wright SH, *et al*: PKC regulation of organic anion secretion in perfused S2 segments of rabbit proximal tubules. *Am J Physiol* 278:F104–F109, 2000
61. Gekle M, Mildenberger S, Sauvaant C, *et al*: Inhibition of initial transport rate of basolateral organic anion carrier in renal PT by BK and phenylephrine. *Am J Physiol* 277:F251–F256, 1999
62. Halpin PA, Renfro JL: Renal organic anion secretion: Evidence for dopaminergic and adrenergic regulation. *Am J Physiol* 271: R1372–R1379, 1996
63. Hohage H, Morth DM, Querl IU, *et al*: Regulation by protein kinase C of the contraluminal transport system for organic cations in rabbit kidney S_2 proximal tubules. *J Pharmacol Exp Ther* 268:897–901, 1994
64. Hohage H, Löhr M, Querl U, *et al*: The renal basolateral transport system for organic anions: Properties of the regulation mechanism. *J Pharmacol Exp Ther* 269:659–664, 1994
65. Miller DS, Sussman CR, Renfro JL: Protein kinase C regulation of p-glycoprotein-mediated xenobiotic secretion in renal proximal tubule. *Am J Physiol* 275:F785–F795, 1998
66. Masuda S, Saito H, Inui K-I: Interactions of nonsteroidal anti-inflammatory drugs with rat renal organic anion transporter, OAT-K1. *J Pharmacol Exp* 283:1039–1042, 1997
67. Besseghir K, Mosig D, Roch-Ramel F: Facilitation by serum albumin of renal tubular secretion of organic anions. *Am J Physiol* 256:F475–F484, 1989
68. Taft DR, Sweeney KR: The influence of protein binding on the elimination of acetazolamide by the isolated perfused rat kidney: Evidence of albumin-mediated tubular secretion. *J Pharmacol Exp Ther* 274:752–760, 1995
69. Szalay L, Bencsáth P, Takács L: Effect of splanchnicotomy on the renal excretion of para-aminohippuric acid in the anesthetized dog. *Pflügers Arch* 367:287–290, 1977
70. Vasilenko VA: The renal function during compensatory hypertrophy (in Russian). *Fiziol Zh SSSR* 49:535–541, 1963
71. Lysov VF: Effect of stimulation of efferent fibers of the splanchnic nerves on renal tubular activity. (in Russian) *Biul Eksp Biol Med* 66:29–32, 1968; (translated to English) *Bull Exp Biol Med* 736–738, 1968
72. Brukhanov VM: Renal transport of organic substances by adrenoreceptor stimulation. (in Russian) *Fiziol Zh SSSR* 63:742–747, 1977
73. Brukhanov VM: Effect of dopamine on renal transport of organic substances in dog. (in Russian) *Fiziol Zh SSSR* 69:1085–1091, 1983
74. Jensen RE, Berndt WO: Epinephrine and norepinephrine enhance p-aminohippurate transport into basolateral membrane vesicles. *J Pharmacol Exp Ther* 244:543–549, 1988
75. Harvey RB: Effect of acetylcholine infused into renal artery of dogs. *Am J Physiol* 211:487–492, 1966
76. Brukhanov VM: Effect of acetylcholine on renal tubular reabsorption of glucose and secretory processes. (in Russian) *Fiziol Zh SSSR* 66:1571–1574, 1980
77. Farah A, Koda F, Frazer M: Studies on the control of the renal tubular transport of p-aminohippurate by the anterior pituitary. *Endocrinology* 58:399–411, 1956
78. Misanko BS, Park YS, Solomon S: Effect of hypophysectomy on p-aminohippurate transport kinetics in rat renal cortical slices. *J Endocrinol* 74:121–128, 1977
79. Hirsch GH, Hook JB: Stimulation of p-aminohippurate transport by slices of rat renal cortex following in vivo administration of triiodothyronine. *Proc Soc Exp Biol Med* 131:513–517, 1969
80. Nepomuceno CG, Little JM: In vitro effects of thyroxine and analogues on the renal uptake of PAH and TEA. *J Pharmacol Exp Ther* 146:294–297, 1964
81. Berkhin EB, Galyuteva GI: Significance of genetic induction in the action of thyreoidin and triiodothyronine on the tubular secretion of the kidneys. (in Russian) *Farmakol Toksikol* 37:590–591, 1974
82. Galyuteva GI: Effect of thyroid hormones on the renal transport of organic substances. (in Russian) *Biul Eksp Biol Med* 79:11–13, 1975 (translated into English) *Bull Exp Biol Med* August:103–105, 1975
83. Bräunlich H: Postnatal development of kidney function in rats receiving thyroid hormones. *Exp Clin Endocrinol* 83:243–250, 1984
84. Bräunlich H: Transport of p-aminohippurate in renal cortical slices of rats of different ages following treatment with thyroid hormones. *Biomed Biochim Acta* 46:251–257, 1987
85. Ortweiler W, Jahn F, Bräunlich H: Increase of ^{14}C-leucine

uptake following stimulation of renal tubular transport processes. *Biomed Biochim Acta* 46:271–276, 1987
86. Bakhteeva VT: The stimulation of organic acid secretion in the kidneys of the frog *Rana temporaria* with the repeated administration of para-aminohippurate and triiodothyronine. (in Russian) *Zh Evol Biokhim Fiziol* 27:392–395, 1991
87. Kippen I, Kurokawa K, Klinenberg JR: Stimulation of p-aminohippuric acid transport in rabbit kidney cortex by parathyroid hormone and adenosine 3′,5′-cyclic monophosphate. *Biochem Pharmacol* 25:219–220, 1976
88. Podevin RA, Boumendil-Podevin EF: Inhibition by cyclic AMP and dibutyryl cyclic AMP of transport of organic acids in kidney cortex. *Biochim Biophys Acta* 35:106–114, 1975
89. Nikitin AI: Effect of insulin on tubular secretion. (in Russian) *Biul Eksp Biol Med* 72:13–15, 1971 (translated into English) *Bull Exp Biol Med* May:1372–1373, 1972
90. Fomenko GF: Effect of hydrocortisone on renal tubular secretory function. (in Russian) *Probl Endokrinol (Mosk)* 15:70–73, 1969
91. Bräunlich H, Rassbach H, Vogelsang S: Stimulation of renal transport of p-aminohippurate in rats of different ages by treatment with adrenocortical steroids. *Dev Pharmacol Ther* 19:1–5, 1992
92. Huang KC, McIntosh BJ: Effect of sex hormones on renal transport of p-aminohippuric acid. *Am J Physiol* 183:387–390, 1955
93. Galyuteva GI: Mechanism of testosterone influence on the renal tubular secretion. (in Russian) *Probl Endokrinol (Mosk)* 20:78–81, 1974
94. Ferguson DM, Matthews BF: Effects of sex, age and removal of gonads on p-aminohippurate uptake by kidney cortex slices in the rat. *J Physiol* 169:24P–25P, 1963
95. Kleinman LI, Loewenstein MS, Goldstein L: Sex difference in the transport of p-aminohippurate by the rat kidney. *Endocrinology* 78:403–406, 1966
96. Bowman HM, Hook JB: Sex differences in organic ion transport by rat kidney. *Proc Soc Exp Biol Med* 141:258–262, 1972
97. Reyes JL, Meléndez E, Alegría A, Jaramillo-Juárez F: Influence of sex differences on the renal secretion of organic anions. *Endocrinology* 139:1581–1587, 1998
98. Hanhijärvi H, Ophang RH, Singer L: The sex-related difference in perfluorooctanoate excretion in the rat. *Proc Soc Exp Biol Med* 171:50–55, 1982
99. Smith AG, Francis JE: Evidence for the active renal secretion of S-pentachlorophenyl-N-acetyl-L-cysteine by female rats. *Biochem Pharmacol* 32:3797–3801, 1983
100. Tanaka Y, Deguchi Y, Ishii I, *et al*: Sex differences in excretion of zenarestat in rat. *Xenobiotica* 21:1119–1125, 1991
101. Terashita S, Sawamoto T, Deguchi S, *et al*: Sex-dependent and independent renal excretion of nilvadipine metabolites in rat: Evidence for a sex-dependent active secretion in kidney. *Xenobiotica* 25:37–47, 1995
102. Tanaka Y, Fujiwara T, Esumi Y: Sex difference in the excretion of zenarestat in mice, rats, dogs, and humans. *Xenobiotica* 22:941–947, 1992
103. Hirsch GH, Hook JB: Maturation of renal organic acid transport: Substrate stimulation by penicillin. *Science* 165:909–910, 1969
104. Hirsch GH, Hook JB: Additional studies on penicillin-induced stimulation of renal PAH transport. *Can J Physiol Pharmacol* 48:550–556, 1970
105. Hirsch GH, Hook JB: Maturation of renal organic acid transport: Substrate stimulation by penicillin and p-aminohippurate (PAH). *J Pharmacol Exp Ther* 171:103–108, 1970
106. Johnson JT, Holloway LS, Heisey SR, *et al*: Substrate stimulation of organic anion transport in newborn dog kidney and choroid plexus. *Biochem Pharmacol* 23:754–758, 1974
107. Hirsch GH, Hook JB: Stimulation of renal organic acid transport and protein synthesis by penicillin. *J Pharmacol Exp Ther* 174:152–158, 1970
108. Ecker JL, Hook JB: Accumulation of p-aminohippuric acid by separated renal tubules from newborn and adult rabbits. *J Pharmacol Exp Ther* 190:352–357, 1974
109. Bond JT, Bailie MD, Hook JB: Maturation of renal organic acid transport in vivo: Substrate stimulation by penicillin. *J Pharmacol Exp Ther* 199:25–31, 1976
110. Bernhardt G, Bräunlich H, Dietze C, *et al*: Beschleunigung der renalen Ausscheidung von p-aminohippursäure bei Ratten verschiedenen Alters durch wiederholte Zufuhr von Fremdstoffen. *Acta Biol Med Germ* 31:423–434, 1973
111. Varshavsky BY, Sazonov VF, Biryulya VN: Pharmacokinetics of penicillin on its repeated administration. (in Russian) *Antibiotiki* 19:981–984, 1974
112. Storch R, Bräunlich H: Stimulierung der renalen Ausscheidung von p-aminohippursäure durch wiederholte Zufuhr von Pharmaka bei jungen und erwachsenen Ratten. *Acta Biol Med Germ* 34:1529–1539, 1975
113. Berkhin EB, Varshavsky BY: Substrate induction of tubular secretion of organic compounds in the kidney. (in Russian) *Dokl Akad Nauk* 220:1463–1466, 1975
114. Stopp M, Hartwich R, Bräunlich H: Enhancement of p-aminohippurate accumulation in renal cortical slices after repeated administration of various organic anionic drugs to rats of different ages. *Experientia* 34:1493–1494, 1978
115. Berkhin EB, Varshavsky BY, Zikov YN: Substrate stimulation of renal tubular secretion of penicillin and cardiotrast in dogs. (in Russian) *Biul Eksp Biol Med* 83:530–531, 1977 (translated into English) *Bull Exp Biol Med* October:625–626, 1977
116. Berkhin EB: New data on renal secretion of organic compounds. (in Russian) *Fiziol Zh SSSR* 64:384–388, 1978
117. Varshavsky BY: Maximal rate of renal tubular secretion of cardiotrast during its continuous intravenous infusion. (in Russian) *Fiziol Zh SSSR* 64:379–383, 1978
118. Hirsch GH, Cowan DF, Hook JB: Histological changes in normal and drug-induced development of renal PAH transport. *Proc Soc Biol Med* 137:116–121, 1971
119. Pegg DG, Bernstein J, Hook JB: Biochemical and ultrastructural correlates of substrate stimulation of renal organic anion transport. *Proc Soc Exp Biol Med* 151:720–725, 1976
120. Vinnichenko LN, Varshavsky BY: Fine structure of the rat kidney proximal tubule epithelium during cardiotrast secretion. (in Russian) *Tsitologia* 22:5–9, 1980
121. Varshavsky BY, Vinnichenko LN: The ultrastructure of the rat kidney proximal tubule epithelium during the substrate stimulation of cardiotrast secretion. (in Russian) *Tsitologia* 22:219–221, 1980
122. Despopoulos A: Renal excretory transport of organic acids: Inhibition by oxypyrimidines. *Am J Physiol* 200:163–166, 1961
123. Støren EJ: Effect of pentobarbital anesthesia on T_m PAH in the dog. *Am J Physiol* 192:387–391, 1958
124. Letteri JM, Wesson LG: Mercaptomerin effect on p-aminohippurate transport in man and pentobarbitalized dog. *Am J Physiol* 206:1379–1383, 1964
125. Støren EJ: Effect of pentobarbital sodium on uptake of PAH by rat kidney cortex slices. *Am J Physiol* 195:343–346, 1958
126. Fomenko GF: Effect of some neurotropic agents on the tubular secretion. (in Russian) *Farmakol Toksikol* 31:67–69, 1968
127. Nikiforov AA, Ostretsova IB: Stimulatory effect of ethanol on weak organic acid uptake in rat renal tubules. *Biochem Pharmacol* 47:821–825, 1994
128. Burg MB, Orloff J: Effect of strophanthidin on electrolyte content and PAH accumulation of rabbit kidney slices. *Am J Physiol* 202:565–571, 1962
129. Maxild J, Møller JV, Sheikh MI: Involvement of Na^+-K^+-ATPase in p-aminohippurate transport by rabbit kidney tissue. *J Physiol* 315:189–201, 1981
130. Dawson MA, Renfro JL: Organic anion secretion by winter flounder renal proximal tubule primary monolayer cultures. *J Pharmacol Exp Ther* 254:39–44, 1990
131. Pakhmurnyi BA: Renal secretory processes under the influence of strophanthin (in Russian), in *Regulation of Renal Function and Water-Salt Metabolism*, edited by Berkhin E, Barnaul, Altai Medical Institute, 1968, pp 17–23
132. Spencer AM, Sack J, Hong SK: Relationship between PAH transport and Na-K-ATPase activity in the rabbit kidney. *Am J Physiol* 236:F126–F130, 1979
133. Berkhin EB: *Renal Secretion of Organic Substances.* (in Russian) Leningrad, Nauka, 1979
134. Bräunlich J: Der Einfluss von Diuretica auf die renale Ausschei-

dung von Wasser and Ionenbei Ratten verschiedenen Alters. II. Inulin-Clearance und maximale tubuläre Ausscheidung von p-aminohippur Säure nach Applikation von Diuretica. *Acta Biol Med Germ* 25:315–323, 1970
135. Zverev YF: Effect of dichlothiazide on the renal transport of organic substances. (in Russian) *Farmakol Toksikol* 41:69–72, 1978
136. Kulikova DA, Rudzit EA: Influence of furosemide on distribution of penicillin in laboratory animals. (in Russian) *Antibiotiki* 17:259–262, 1972
137. Bartel C, Wirtz C, Brändle E, *et al*: Interaction of thiazide and loop diuretics with the basolateral para-aminohippurate transport system in isolated S_2 segments of rabbit kidney proximal tubules. *J Pharmacol Exp Ther* 266:972–977, 1993
138. Bresler VM, Natochin YV: Inhibition of fluorescein secretion in the proximal renal tubule of the frog by diuretics. (in Russian) *Biul Eksp Biol Med* 75:67–69, 1973 (translated into English) *Bull Exp Biol Med* 75:675–677, 1973
139. Zverev YF: Effect of furosemide on the renal transport of organic substances. (in Russian) *Biul Eksp Biol Med* 84:436–438, 1977 (translated into English) *Bull Exp Biol Med* March:1436–1438, 1978
140. Kuvshinnikova VA: Effect of retabolil on the renal tubular secretion. (in Russian) *Biul Eksp Biol Med* 81:312–313, 1976 (translated into English) *Bull Exp Biol Med* August:364–365, 1976
141. Varshavsky BY, Verlinsky SG, Biryulya VA: Effect of potassium orotate on the transport of organic substances in the kidneys. (in Russian) *Biul Eksp Biol Med* 77:58–60, 1973 (translated into English) *Bull Exp Biol Med* August:150–152, 1974
142. Kluwe WM, McCormack KM, Hook JB: Chemical induction of p-aminohippuric acid transport in renal cortical slices from adult and immature rabbits. *J Pharmacol Exp Ther* 205:743–750, 1978
143. Berkhin EB, Lampatov VV, Ulyanov GP: The induction of monooxygenase system and renal transport of xenobiotics. (in Russian) *Physiol J SSSR* 73:685–688, 1987
144. Astafeva EP, Berkhin EB, Ulyanov GP: Effect of zixorin on diuresis and renal transport of xenobiotics (in Russian). *Biul Eksp Biol Med* 104:602–603, 1987 (translated into English) *Bull Exp Biol Med* April:1591–1593, 1988
145. Berkhin EB, Varshavsky BY, Kuvshinnikova VA: Role of genetic induction in renal tubular secretion. (in Russian) *Physiol J SSSR* 63:458–462, 1977
146. Dominguez JH, Hale CC, Qulali M: Studies of renal injury. I. Gentamicin toxicity and expression of basolateral transporters. *Am J Physiol* 270:F245–F253, 1996
147. Fukuda Y, Malmborg A-S, Aperia A: Gentamicin inhibition of Na^+, K^+-ATPase in rat kidney cells. *Acta Physiol Scand* 141:27–34, 1991
148. Fomenko GF: Effect of 6-mercaptopurine on secretory function of the kidneys. (in Russian) *Biul Eksp Biol Med* 67:58–60, 1969 (translated into English) *Bull Exp Biol Med* 67:276–277, 1969
149. Brukhanov VM: Effect of cyclophosphamide on tubular secretion in the kidneys. (in Russian) *Biul Eksp Biol Med* 70:60–63, 1970 (translated into English) *Bull Exp Biol Med* 70:784–786, 1970
150. Ammer U, Natochin Y, David C, *et al*: Cisplatin nephrotoxicity: Site of functional disturbance and correlation to loss of body weight. *Ren Physiol Biochem* 16:131–145, 1993
151. Rahman A, Roh JK, Preuss HG: Comparative nephrotoxicity of tetraplatin and cisplatin in rats. *Nephron* 64:289–295, 1993
152. Goldstein RS, Noordewier B, Bond JT, *et al*: Cis-Dichlorodiamineplatinum nephrotoxicity: Time course and dose response of renal functional impairment. *Toxic Appl Pharmacol* 60:163–175, 1981
153. Inselmann G, Blöhmer A, Kottny W, *et al*: Modification of cisplatin-induced renal p-aminohippurate uptake: Alteration and lipid peroxidation by thiols, Ginkgo biloba extract, deferoxamine and torbafylline. *Nephron* 70:425–429, 1995
154. Borch RF: The nephrotoxicity of anticancer drugs, in *Renal Disposition and Nephrotoxicity of Xenobiotics*, edited by Anders M, Decant W, Henschler D, Oberleithner H, Silbernagl S, San Diego, Academic Press, 1993, pp 289–310
155. Zaruba K: Effect of local irradiation of the kidneys on the renal function of the dog. *Radiat Res* 35:661–667, 1968
156. Brukhanov VM: Renal secretory function after x-ray radiation and preventive administration of cystamin. (in Russian) *Radiobiologia* 11:451–454, 1971
157. Buss WC, Stepanek J, Bennett WM: A new proposal for the mechanism of cyclosporine A nephrotoxicity. *Biochem Pharmacol* 38:4085–4093, 1989
158. Walker RJ, Lazzaro VA, Duggin GG, *et al*: Cyclosporin A inhibits protein kinase C activity: A contributing mechanism in the development of nephrotoxicity? *Biochem Biophys Res Commun* 160:409–415, 1989
159. Berkhin EB: Effect of immunostimulants on tubular secretion of xenobiotics in the kidney. (in Russian) *Biul Eksp Biol Med* 100:584–586, 1985 (translated into English) *Bull Exp Biol Med* April:1549–1551, 1986
160. Berkhin EB, Lampatov VV, Ulyanov GP: Effect of 5-oxymethyluracil and dimephosphon on renal tubular transport of xenobiotics. (in Russian) *Farmakol Toksikol* 50:37–38, 1987
161. Arion VY, Berkhin EB, Galyuteva GI, *et al*: Effect of tactivin on diuresis and tubular secretion of cardiotrast in the kidney. (in Russian) *Biul Eksp Biol Med* 107:264–266, 1989 (translated into English) *Bull Exp Biol Med* August:283–285, 1989
162. Hirsch GH, Hook JB: Stimulation of renal p-aminohippurate transport by folic acid. *Biochem Pharmacol* 18:2274–2278, 1969
163. Fujimoto Y, Fujita T: Effect of lipid peroxydation on p-aminohippurate transport by rat kidney cortical slices. *Br J Pharmacol* 76:373–379, 1982
164. Natochin YV: Integration and modulation of functions in the physiology of nephrone cell. (in Russian) *Fiziol Zh Im I Sechenova* 79:8–17, 1993
165. Fleck C, Bräunlich H: Factors determining the relationship between renal and hepatic excretion of xenobiotics. *Arzneimittel-Forsch* 40:942–946, 1990
166. Sergeev PV, Shimanovskii NL, Zaretskii DV: The molecular mechanisms of the elimination of organic anions by the liver. (in Russian) *Eksp Klin Farmakol* 56:62–69, 1993
167. Oude Elferink PPJ, Jansen PLM: The role of the canalicular multispecific organic anion transporter in the disposal of endo- and xenobiotics. *Pharmacol Ther* 64:77–97, 1994
168. Yamazaki M, Suzuki H, Sugiyama Y: Recent advances in carrier-mediated hepatic uptake and biliary excretion of xenobiotics. *Pharm Res* 13:497–513, 1996
169. Miller DS, Stewart DE, Pritchard JB: Intracellular compartmentation of organic anions within renal cells. *Am J Physiol* 264:R882–R890, 1993